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Controversial Nutrients That Potentially Affect Preterm Neurodevelopment: Essential Fatty Acids and Iron

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Although all nutrients are needed for normal fetal and postnatal development, small preterm infants are particularly susceptible to nutrient deficiencies. The potential for immediate and long-term consequences of deficiency varies among nutrients. Essential fatty acids and iron are of particular interest because both are commonly deficient in the preterm infant, excessive or inadequate intakes are both of concern, and both are crucial to normal CNS development with the potential for long lasting effects that extend beyond the period of dietary insufficiency. Although seemingly diverse in physiologic roles, advances in the understanding of iron and essential fatty acid metabolism provide an exemplary illustration how different nutrients interact to support normal growth and development.

The potential for adverse effect of inadequate or excess intake of any nutrient on any organ system is based on the timing, dose and duration of exposure (1). The vulnerability of a particular organ thus depends on the concurrence of two factors; the presence of a critical (or sensitive) period of growth and development that is dependent on the nutrient in question; and deficiency of the nutrient in the population at the time of this sensitive period. Effects that last beyond the period of exposure result from deviations from the normal developmental trajectory, involving morphologic process for example neuritogenesis, myelination, expression of genes for key proteins or endocrine factors that regulate development, that are incompletely recovered at some later stage with restoration of normal nutrition. The brain between 6 mo postconception and 1 y of age undergoes a remarkable transformation from a relatively primitive, poorly sulcated and gyrated structure into a complex, integrated organ. Important neurodevelopmental processes at this time include the onset of myelination, organization of neurotransmitter systems, dendritic arborization and selective pruning, and synaptogenesis particularly in the visual system and the hippocampus (Fig. 1) (2). Iron and essential fatty acids impact on these developmental processes at multiple levels that have the potential for lasting effects in preterm infants inadequately nourished with these nutrients.

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ESSENTIAL FATTY ACID REQUIREMENTS OF THE PRETERM INFANT

Docosahexaenoic acid (DHA, 22:6n-3) and arachidonic acid (ARA, 20:4n-6) are required by preterm infants to support growth and development. DHA and ARA are formed from the essential fatty acids, linoleic acid (LA,18:2n-6) and α-linolenic acid (LNA,18:3n-3), respectively, by elongation and desaturation (3) and are the major polyunsaturated fatty acids in fetal plasma. In contrast, LA and LNA are the most abundant n-6 and n-3 fatty acids in human milk, infant formula and IV lipids. Plasma LA increases, while ARA and DHA decrease rapidly with the initiation of feeding. LA and LNA are mutually competitive and their metabolism is inhibited by products of the autologous and opposing fatty acid series (4). Thus, inappropriately high intakes of one of the n-6 and n-3 fatty acids can have deleterious effects on other n-6 and n-3 fatty acids. DHA and ARA are present in membrane phospholipids where they regulate membrane functions, and from which they are released to act directly or as precursors to molecules that modulate cell growth, inter- and intra-cellular communication and protein function (3). DHA is selectively accumulated in specific tissues that include the retina and brain grey matter. Depletion of DHA from the brain and retina results in reduced visual function, cognitive and behavioral abnormalities, altered monaminergic neurotransmitter metabolism, and decreased membrane protein and receptor activities (3). The monoamines dopamine and serotonin are important in many of the cognitive and behavior advances of early childhood; their synthesis is regulated by the iron dependent tyrosine and tryptophan hydroxylase, respectively. ARA is found in membranes throughout the body, fulfills the role of n-6 fatty acids in growth, and is the precursor for eicosanoids and other signal molecules. N-6 and n-3 fatty acids also regulate carbohydrate and lipid metabolism through effects on gene expression involving steroid regulatory element binding proteins and peroxisomal proliferator activated receptors (3,5,6). The desaturases required for synthesis of ARA and DHA, and delta 9 desaturase required for synthesis of oleic acid (18) (which is the major monoenoic fatty acid in brain white and grey matter), are iron dependent enzymes.

Essential fatty acids in the fetus and preterm infant. The higher ARA and DHA and lower LA in fetal, (rather than maternal or infant) plasma (7,8) maybe explained in part by

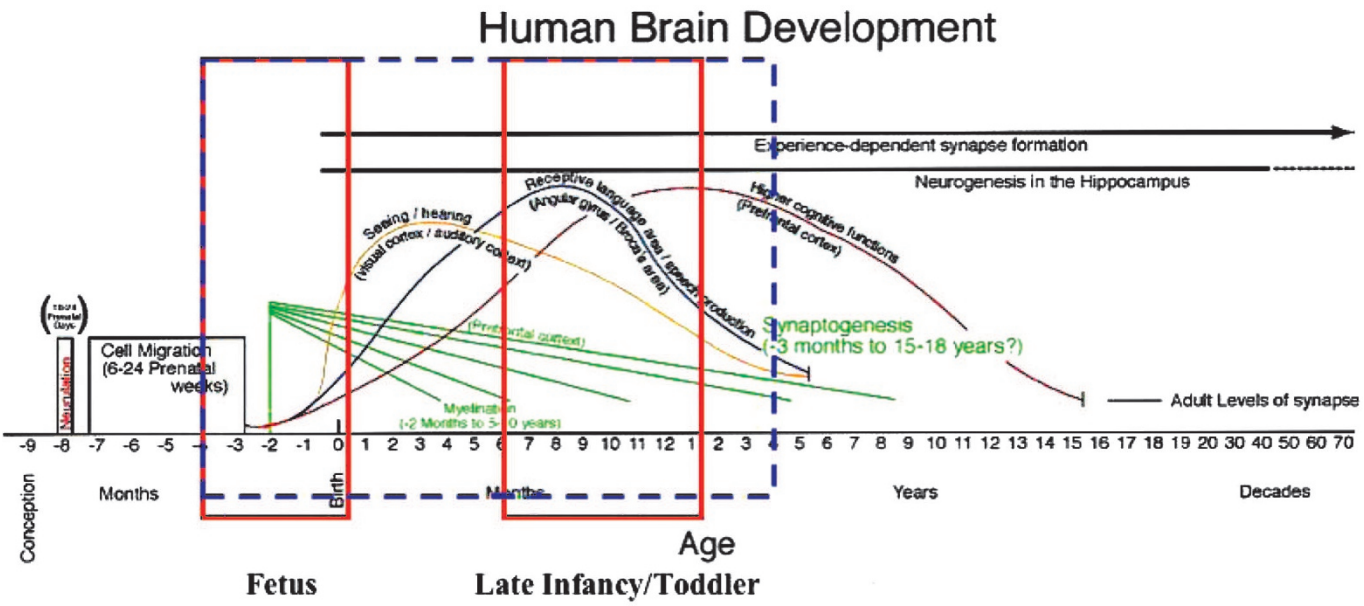

Figure 1. Risk periods for alterations in essential fatty acid (blue box) and iron (red boxes) metabolism during early human brain development. Brain development chart adapted from reference 2.

placental fatty acid binding and transport proteins that favor transfer of ARA and DHA (8,9). Other differences in plasma lipids before and after birth include the high ARA in fetal cholesterol esters, presence of high-density lipoprotein (HDL) as a major lipoprotein, low chylomicrons and very low-density lipoprotein (VLDL), and transport of ARA and DHA by α-fetoprotein (8). Whether the low LA relative to ARA and DHA is fetal plasma is important in facilitating optimal tissue delivery of these fatty acids is unclear. However, the possibility that high LA may inhibit tissue DHA accumulation has been raised (8,10).

LA and LNA are the major n-6 and n-3 fatty acids in human milk fat (mean 12% LA, 1.4% LNA, 0.4% ARA, 0.2% DHA), formula (16–20% LA, 1,5–2.3% LNA, 0.4–0.6% ARA, 0.2–0.3% DHA) and IV lipids (53% LA, 7% LNA, 0.2% ARA, 0.2% DHA in 20 g/dL soybean triglyceride emulsions containing egg phospholipid) (11,12). The desaturation of LNA to DHA in humans, including infants, is low with $<$1% to 9% of a dose of isotopically labeled LNA converted to DHA (13). However, LNA conversion appears to be at least as high in preterm as term infants (14). Increasing the LNA content of formula has little effect in increasing blood lipid DHA, but feeding with ARA or DHA is efficacious in increasing blood and tissue ARA and DHA, respectively (10,15,16). Thus, DHA is clearly more efficacious for tissue DHA accretion than the LNA precursor (17,18). There is no evidence that infants are unable to form adequate ARA, except possibly following eicosapentaenoic acid (EPA, 20:5n-3) and DHA supplementation which could antagonize ARA synthesis or acylation.

Studies with preterm infants supplemented with ARA and DHA. Several sources of DHA (fish oils, egg lipids and single cell (algal) oil), and ARA (egg lipids and single cell (fungal) oil), have been considered for addition to infant formula. Early studies found evidence of reduced growth and lower peripheral nerve conduction velocities in preterm infants fed formula with DHA without ARA (19–22). The lower growth was presumed to be due to suppression of ARA by EPA and/or DHA. Subsequent studies have not found lower growth in infants fed formulas with both DHA and ARA (16,23,24). Rather, higher growth in preterm infants fed formula with ARA and DHA from single cell oils and a positive relation between plasma ARA and preterm infant growth has been shown (16,25). A recent study has noted lower growth at 18 mo of age in preterm infants fed formula with 0.4% γ linolenic acid (18:3n-6), 0.3% ARA and 0.17% DHA from egg lipids, which included cholesterol (26). These findings suggest different sources of ARA and DHA can differ in their effects on preterm infant growth and development.

Several studies concur that dietary DHA increases the early development of visual acuity in preterm infants (23,27). An advantage in tests of mental and language development has also been reported in small preterm infants $<$1,250g birthweight fed formula with DHA and ARA (23). The improved visual and neural development in the latter studies show that 1.2% energy as LNA present in the unsupplemented formula does not meet the n-3 fatty acid requirements of preterm infants.

Essential fatty acid requirements. One approach to address the nutrient needs of preterm infants is to match the plasma nutrient levels of the fetus. However, fetal plasma is characterized by low VLDL and LDL, low LA and high ARA and DHA (8). Human milk, infant formula, or IV lipids are provided to attain growth rates approaching that of the third trimester fetus, and triglyceride-rich lipoproteins high LA emerge as a major plasma lipid transport particle. Feeding with triglycerides high in LA as a major energy source make it unlikely that plasma ARA and DHA levels similar to the third trimester fetus can be achieved in parenterally or enterally fed infants.

Alternatively, an estimate of needs can be derived from estimates of fatty acid accretion in fetal tissue. Autopsy tissue analyses have estimated an accretion of 552 mg/d n-6 fatty acids and 67 mg/d n-3 fatty acids during the last trimester of gestation (28). Most of the n-3 fatty acids accumulated is DHA, while fetal liver and adipose tissue contain about 2-fold more ARA than LA (29). Fetal brain accretion has been estimated as 5.8 mg n-6 and 3.1 mg n-3 fatty acids/d, representing about 1.1% and 4.65% total body accretion. It is not known if the fetal brain is protected during limited DHA availability; however, prenatal n-3 fatty acid deprivation does result in a large deficit in fetal brain DHA in animals (30). Estimation of the essential fatty acid intakes of preterm infants fed at 120 mL/kg with human milk or formula, or given IV lipid (Table 1) shows the marked overabundance of LA and LNA compared with the estimated fetal accretion. Assuming 5% or 10% LNA is converted to DHA, a theoretical estimate of the total potential DHA available from 120 mL/kg/d milk or formula, or 3g/kg/d IV lipid is 11–28 mg DHA, which is less than 50% of the estimated *in utero* accretion of 60 mg/d. Although these estimates are based on limited data, and growth and tissue DHA accretion are not linear, it is apparent that current approaches to lipid nutrition for preterm infants are likely to result in marked differences in tissue fatty acids from that achieved *in utero*.

IRON AND BRAIN DEVELOPMENT

Iron deficiency potentially affects multiple developmental brain processes including myelination (31), monoamine metabolism (32), energy metabolism (33), and hippocampal dendritic growth (34), most of which are dependent on iron-containing hemoproteins or iron-sulfur compounds that are compromised by iron deficiency. The effect on myelination (31) is due in part to effects on iron-dependent enzymes in fatty acid synthesis pathways (35) and oligodendrocyte function (31). Hypomyelination would be expected lead to slower nerve conduction velocity, an effect manifested in 6-mo-old human infants by abnormal auditory brainstem evoked responses while iron deficient (36) and following iron repletion (37). Early iron deficiency in the rat results in reduced hippocampal cytochrome *c* (a hemoprotein) concentrations and cytochrome *c* oxidase activity, thus altering energy utilization in a brain region that subserves recognition memory. Iron deficient human neonates show electrophysiologic evidence of reduced recognition memory at birth while iron deficient (38) and following iron repletion (39). Early iron deficiency in rats also has profound effects on the developing dopaminergic system particularly in the basal ganglia, a brain region that subserves procedural memory and motor function (40). In humans, early postnatal iron deficiency alters motor movement patterns while infants are iron deficient and long-term striatal-frontal cognitive functions (41,42). Ultimately, the integration of all these negative brain effects compromise later integrated cognitive performance (41). For example, infants born with cord serum ferritins in the lowest quartile have poorer school performance than those in the middle quartiles (43).

Several common pathologic conditions during gestation affect newborn brain iron status. These include severe maternal iron deficiency, intrauterine growth-retardation due to maternal hypertension, premature delivery and gestational or pregestational maternal diabetes mellitus. The first three result in decreased iron delivery to the fetus while the latter results in decreased delivery and a redistribution of iron into the red cell mass (and away from the brain) within the fetus (44,45). Fetal iron status will be compromised when the mother's Hb concentration is less than 85 g/L, although recent evidence suggests that alterations in iron metabolism occur at Hb concentrations as high as 105 g/L (46). Although profound maternal iron deficiency is relatively rare in developed nations, the worldwide rate approaches 30 to 50%. Decreased placental function due to maternal hypertension results in intrauterine growth retardation and iron deficiency. Fifty percent of growth retarded infants have newborn serum ferritin concentrations below the 5th percentile (<60 μg/L) (47). A conservative estimate would predict that 75,000 infants per year are affected in the United States. At autopsy, intrauterine growth retardation (IUGR) infants have a 33% reduction in brain iron (48). In pregnancies complicated by diabetes, the degree of maternal glucose intolerance drives the degree of iron deficiency (44,45). Fetal hyperglycemia and hyperinsulinemia increase fetal oxygen consumption by 15 to 30% (49,50), rendering the fetus chronically hypoxemic and stimulating compensatory erythropoiesis (51). The human (and sheep) placenta do not appear to compensate for the increased iron need for this augmented erythropoiesis (52), forcing the fetus to prioritize available iron to the red cell mass over the brain (44,45,53). Up to 65% of infants of diabetic mothers (150,000 newborns/y in the US) are affected. At autopsy, IDMs (infants of diabetic mothers) have a 40% reduction of brain iron content (44).

Table 1. *Estimated intake of essential fatty acids from human milk, infant formula or intravenous lipids in the preterm infant*

	Human milk* 120 mL/kg/day	Preterm formula** 120 mL/kg/day	I.V. Lipid† 0.5 g/kg	I.V. Lipid† 1.0 g/kg	I.V. Lipid† 3.0 g/kg	Intrauterine‡
LA (18:2n-6)	530	710–880	265	530	1590	184
ARA (20:4n-6)	31	18–27	1	2	6	368
LNA (18:3n-3)	60	71–98	36	72	216	7
DHA (22:6n-3)	8	8–16	1	2	6	60
ΣDHA + LNA equivalent§	(11–14)	(12–25)	(2.8–4.6)	(5.6–9.4)	(18–28)	

* Based on 12% LA, 1.4% LNA, 0.7 ARA, 0.2% DHA and 3.7 g fat/dL milk (11).

** Range represents preterm formula with 16–20% LA, 1.6–2.2% LNA, 0.4–0.6% ARA, 0.2–0.4% DHA.

† 100% soybean oil in a 20% emulsion with egg phospholipid as emulsifier (18).

‡ Intrauterine estimate assumes tissue ARA twofold higher than LA and DHA equivalent to 90% of total n-3 fatty acids (28, 29).

§ Estimated total potential DHA, assuming 5–10% LNA converted to DHA.

There is evidence that IDMs and IUGRs have altered short and long-term neurologic processing (38,39,54,55).

Prematurity places the developing brain at risk for iron deficiency and iron overload. The fetus accretes iron primarily during the last trimester of pregnancy. Infants born prematurely have lower total body iron contents than those born at term. After birth, factors that lead to negative iron balance include phlebotomy, a rapid catch-up growth rate that necessitates equally rapid expansion of the red cell mass, more conservative transfusion practices (and the use of recombinant human erythropoietin), and human milk feeding without iron supplementation (56). Iron deficiency is common and occurs earlier in the postdischarge period in preterm infants (57), a finding that prompted the recommendation that preterm infants be supplemented with 2–4 mg/kg/d of iron beginning as early as 2 wk and no later than 2 mo of postnatal life (58). It remains controversial whether premature infants in the newborn intensive care unit are iron deficient. Recent studies have shown elevated zinc protoporphyrin/heme ratios in predischarge premature infants who are rapidly growing (59,60), suggesting that iron availability is limiting the ability of these infants to synthesize Hb. A recent study also demonstrates that preterm infants with ferritin concentrations in the lowest quartile at the end of their neo-natal intensive care unit hospitalization have an increased rate of abnormal neurologic reflexes (61). Although it remains to be determined whether these changes in brain function are long-lasting, this study is the first to link iron deficiency and abnormal neurodevelopment in this population.

Finally, one must consider the potential neurologic hazards of iron overload in preterm infants. While it is clear that iron potentially plays a large role in reperfusion injuries following birth asphyxia (62), the role of *nutritional* iron in brain injury in humans remains unproven. Nevertheless, the premature infant's brain may be at high risk for iron overload because of serum iron binding capacity, immature anti-oxidant systems and rapidly growing tissues and the exposure to IV iron and multiple red cell transfusions (63). No study has convincingly demonstrated that nutritional iron overload contributes to adverse neurodevelopment in preterm infants.

CONCLUSION

This review has highlighted recent advances in the biology of the long chain polyunsaturated fatty acids, particularly DHA, and iron. Both DHA and iron are required for normal biochemical and functional development of the CNS. When imposed at critical periods of development, deficiency of DHA or iron results in deficits in monoamine metabolism (17,30,32), and decreased performance on tests of cognitive performance (19,38,41,43); both nutrients are also involved in normal membrane lipid biosynthesis including myelination (31,35,64). In animal models, iron deficiency and n-3 fatty acid deficiency have been studied in isolation; although in clinical practice, small preterm infants are frequently compromised with respect to nutrition with both these nutrients. The essential role of iron in fatty acid desaturation and monoamine synthesis raise questions of whether or not iron deficiency further compounds the adverse effects of poor DHA and ARA status on the growth and development of preterm infants. DHA and ARA are found only in animal tissues, which also provide heme iron. The greater bioavailability of heme than nonheme iron and efficacy of dietary DHA compared with its LNA precursor which, like nonheme iron, is present in plant foods, raise additional research questions on the co-morbidity of inadequate DHA and iron in many of the world's children.

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